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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,979	DE JONG ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57,59,61-83 and 141-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-57,59,61-83 and 141-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a reply to the "AMENDMENT" of 22 September 2003 (hereinafter, 22 September Paper) filed in reply to the Non-Final Office Action mailed 25 March 2003 (hereinafter, 25 March Office Action). Claims 1-83 and 140-143 were considered in the 25 March Office Action. Claims 58, 60 and 140 were canceled, claims 1, 50, 59, 61-65 and 141 were amended and claims 144-147 were added in the 22 September Paper. Claims 1-57, 59, 61-83 and 141-147 are pending and under consideration.

Response to Amendment

Rejection of claims 58, 60 and 140 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 112

Rejection of claims 1-26, 28-33, 38, 39, 41-48, 53-57, 65, 69, 71-76 and 141 under 35 U.S.C. 112, first paragraph, as lacking adequate written description is withdrawn.

Claims 1-57, 59 and 61-83 stand rejected and newly added claims 144-147 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record and herein below in the response to arguments.

Rejection of claim 50 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 7, 9, 10, 12-14, 30-32 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Strauss *et al.* (1992) *EMBO J.* 11:417-422 is withdrawn.

Rejection of claims 1, 2, 9-17, 19, 26-28, 30-32, 61-64, 142 and 143 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (1997) *Invest. Radiol.* 32:723-727 is withdrawn.

Rejection of claims 1, 9, 10, 12-14, 30-32, 61-66, 70 and 72 are under 35 U.S.C. 102(b) as being anticipated by McDonald *et al.* (1998) U.S. Patent No. 5,837,283 is withdrawn.

Rejection of claims 60-64 under 35 U.S.C. 102(b) as being anticipated by Hadlaczky *et al.* (February 2000) U.S. Patent No. 6,025,155 is withdrawn.

Claims 1, 3-10, 12-14 and 30-33 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hadlaczky *et al.* (February 2000) U.S. Patent No. 6,025,155 for reasons of record and herein below in the response to arguments.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 1-57, 59 and 61-83 were rejected and newly added claims 144-147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a

method for introducing a nucleic acid into a cell *in vitro*, does not reasonably provide enablement for *ex vivo* or *in vivo* gene transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims were rejected on the grounds that, because the specification clearly indicates that gene therapy is within the scope of the claimed invention, the disclosure fails to enable the full scope of the claims. It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation.

> Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

In response, Applicant first appears to deny that gene therapy is within the scope of the claims. Applicant states, "all of the instant claims are directed to methods for delivering nucleic acid molecules into cells, not methods of gene therapy." But then acknowledges, "the uses of nucleic acid delivery, including gene transfer for gene therapy, constitute only a subset of the embodiments that are within the scope of the subject matter as instantly claimed" (first full paragraph on page 20). Given that the specification clearly contemplates *ex vivo* and *in vivo* gene therapy applications for the methods described therein and that the claims are not so limited as to exclude *ex vivo* and *in vivo* gene therapy from the scope of the claims, the claims clearly encompass gene therapy. Furthermore, the claims are not limited to introducing a large nucleic

acid molecule comprising any particular transgene. Thus, the claims are generic to therapy of any condition by introducing a large nucleic acid molecule into a cell. Therefore, enablement for the full scope of the claimed subject matter requires that gene therapy be generally enabled.

Applicant asserts that the specification contemplates numerous utilities in medical, pharmaceutical, biological and technology-related research fields. Applicant urges, "the specification teaches methods of nucleic acid delivery for use in, but not limited to, the above-mentioned fields, including types of delivery agents, methods of using these delivery agents to deliver a nucleic acid molecule to a cell, and methods of introducing nucleic acids to cell types and subjects, including *in vitro*, *ex vivo* and *in vivo* delivery methods" (page 22). However, while it is true that the specification teaches how to deliver a nucleic acid into a cell, methods of delivering nucleic acids into cells had been available for many years before the instant application was filed. In spite of this, attempts at *ex vivo* and *in vivo* gene therapy have generally failed to produce a useful result.

It should also be pointed out that the specification also fails to provide an enabling disclosure for the claims as they broadly encompass the *in vivo* production of pharmaceuticals. At the time of filing recombinant production of proteins in mammals for pharmacological use was not routine. In reviewing the relevant literature, Houdebine (*Transgen. Res.* (2000) 9:305-320) describes a myriad of obstacles that have been encountered by artisans seeking to express recombinant proteins in mammals at pharmaceutically relevant levels. In the abstract, Houdebine identifies three major sources of unpredictability in the art. First is the unpredictability of transgene expression; second is the unpredictability of proper posttranslational modification; and third is the unpredictable effects of high-level recombinant expression on the host mammal.

Houdebine teaches, "the mammary gland is presently the only really available animal bioreactor" (page 315, column 1, paragraph 7). Thus, methods for pharmaceutically relevant production or recombinant proteins in mammalian organs and tissues outside of mammary gland were unavailable to the skilled artisan. With regard to production of pharmaceutical proteins in milk, Houdebine teaches, "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (paragraph bridging pages 309-310). In the paragraph bridging the left and right columns on page 311, Houdebine teaches that even the best mammary-specific promoters available as of 2000 provided inconsistent and unpredictable results when used for expression of recombinant proteins *in vivo*. Houdebine further teaches that proper posttranslational processing of proteins expressed at pharmaceutically relevant levels is often unpredictable because the mechanisms are dependent on cellular enzymes that are present at variable concentrations in different cell types (paragraph bridging columns 1 and 2 on page 313). Importantly, because proper glycosylation is vital for pharmacological activity of many proteins, Houdebine teaches that mammary cells do not always glycosylate recombinant proteins in an appropriate manner even when the protein is naturally secreted in milk in a glycosylated form (see the example of bile salt-stimulated lipase presented in the second full paragraph in the right column on page 313). Houdebine teaches that the reasons why some proteins are not correctly glycosylated are particularly complex and might be related to the superphysiolgical production of the recombinant protein. Furthermore, in the paragraph bridging columns 1 and 2 on page 310, Houdebine teaches that obtaining high-level expression of proteins that are not naturally secreted is particularly problematic.

When viewed as a whole, the teachings of Houdebine, which are based on a review of the state of the art at approximately the time the instant application was filed, clearly show that obtaining pharmaceutically useful expression of a protein in a mammal was only enabled for a limited set of proteins in mammary tissues, and production of pharmaceutically useful amounts of any given protein in mammary tissue was unpredictable. The method steps set forth in the claims are generic to the *in vivo* production of any protein in any animal, yet the teachings of the specification, discussed in the previous Office Action, stop well short of providing general enablement for such a broad scope.

With regard to delivery agents, applicant asserts, "the specification teaches that the delivery methods can be used in any cell type, tissue, organ or subject" (page 22). Again, however, delivery methods capable of providing gene transfer into a wide range of cell types, tissues, organs or subjects were well known in the art at the time of filing. However, in spite of this, applications such as gene therapy and pharmaceutical production of proteins *in vivo* were far from routine at that time. Further, there is no evidence that the teachings of the specification, which provide detailed guidance only for the method practiced *in vitro*, address the art recognized obstacles to developing effective gene therapy and *in vivo* protein expression methods such that these applications would be generally enabled.

As regards *ex vivo* transfer in particular, Applicant urges, "it is taught that methods for *ex vivo* therapy encompass transfecting cells in vitro followed by selection and then by introduction of cells into the body of a subject" and "the specification teaches selection of cells. For example, the specification teaches that nucleic acid molecules can produce a protein that confers drug-resistance, such as hygromycin" (page 23). As regards *in vivo* transfer in particular, Applicant

asserts, "[t]he specification teaches methods for *in vivo* delivery of nucleic acid molecules. Examples of such methods taught by the specification include the application of delivery agents to the target cells in the body of a subject such as an organ, a tumor, a tissue or joint, followed by application of the nucleic acid molecules" (page 24). Again, these particular aspects of *ex vivo* or *in vivo* gene therapy were routine in the art at the time of filing, yet therapeutic application of gene transfer methods remained far from routine.

Applicant points out that the specification teaches methods for the application of *in vivo* and *ex vivo* delivery to gene therapy, citing discussion of factors that will influence dosage such as route of administration, age and weight of the subject and the delivery agents used. However, these teachings are simply recitations of basic pharmacological principles, which were well known in the art at the time of filing. Yet, in spite of the fact that such principles were generally understood, gene therapy could not be routinely achieved at the time of filing. None of the teachings cited by Applicant represent a significant advance in the therapeutic application of gene transfer methods.

Next, Applicant again asserts that the specification teaches numerous applications besides gene therapy for use with the claimed methods and that the enablement rejection is based on the improper importation of "gene therapy" as a limitation of the claims. Applicant urges, "the claims are to methods of nucleic acid delivery, not methods of gene therapy" (page 26). However, this statement seems at odds with Applicant's earlier admission that gene therapy does constitute a subset of the embodiments that are within the scope of the subject matter, and the requirement under 35 U.S.C. §112, first paragraph, that the full scope of the claimed subject matter be enabled (*Id.*).

Next, Applicant appears to argue that gene therapy was indeed enabled at the time of filing. Applicant cites numerous publications related to various methods of transferring nucleic acids into cells, preparing nucleic acids for transfer, expressing reporter genes and detection of labeled nucleic acids. Applicant argues, "it is not unpredictable that nucleic acid molecules, including large nucleic acid molecules can be delivered to cells according to the steps of the instant method" (page 30). It is acknowledged that methods of transferring nucleic acids into cells had been available for more than 20 years prior to the filing date of the instant application. It is also acknowledged that the instant application teaches how to introduce a large DNA into a cell *in vitro.* In spite of this, it would not have been possible to practice the instant claimed method to the extent it broadly encompasses *ex vivo* and *in vivo* gene therapy without engaging in undue experimentation because achieving therapeutic effect by gene transfer was far from routine at the time of filing.

In the remainder of the response, Applicant addresses the publications cited in the previous Office Action as evidence for the unpredictability of extending the teachings disclosed in the instant application such that they are broadly applicable to methods of *in vivo* and *ex vivo* gene therapy. First, Applicant criticizes the reliance upon post-filing date references to establish a lack of enablement as improper (page 32). However, the logic behind this statement is unclear because, although evidence that a method was enabled at some point after filing of an application does not necessarily indicate enablement at the time of filing, evidence that a method was not enabled at some point after filing is clearly probative of the state of the art at the time of filing.

Applicant also criticizes the pre-filing art as "having no bearing on the predictability of delivering a nucleic acid molecule to a cell for gene therapy or any other purpose as of the filing

date, March 2001" (page 32). By way of clarification, discussion of the relevant art in the previous Office Action is structured to demonstrate that many obstacles to obtaining therapeutic effect using any gene transfer method were recognized in the art even early in the development of gene therapy methods and to show that, at the time the instant application was filed, many of these obstacles remained intractable. The state of the art at the time of filing must be evaluated based on the teachings found in the art as a whole and dismissal of individual references as irrelevant because they were published before or after the application filing date is not persuasive.

Also, at several points in discussing the references Applicant asserts that the art recognized obstacles to obtaining adequate gene transfer to produce therapeutic effect are addressed by the instant invention. This argument is not deemed persuasive because there is nothing on the record to indicate that the method disclosed in the instant application is any better than the technologies that were available to the skilled artisan even in the early days of gene therapy.

At several points in discussing the art Applicant points to statements indicating enthusiasm for the future of gene therapy as evidence for enablement. These arguments are not deemed persuasive because recognition that a method might one day be enabled, or even definitive statements that the method will one day be enabled, is not evidence that the method is routinely available at the time of filing.

Applicant also asserts that the relevant standard for enablement is not that of an established, fully optimized, clinical course of treatment; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, as long as it

provides sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification. Applicant's point is taken; however, for the reasons set forth in the previous office action and herein, the skilled artisan would not be able to make and use the full scope of the claimed invention at least insofar as it encompasses methods of *ex vivo* and *in vivo* gene therapy or the production of pharmaceuticals in animals.

Applicant further argues in several places that the Examiner, in asserting the unpredictability of the art of gene therapy, has equated "limitations" with "unpredictability" and submits that although methods of gene therapy may be associated with certain limitations and limited success, this does not establish the art as unpredictable. Applicant urges that, with respect to methods of gene therapy, the well-studied, -identified and -characterized limitations of the art, as determined through years of research make the methods all the more predictable. This argument has been fully considered but is not deemed persuasive. The unpredictability established in the Office Action has to do with the expectation that, given the teachings found in the specification and in the relevant art, it would be readily apparent to the skilled artisan how to make the full scope of the claimed subject matter. Applicant seems to be arguing that because the skilled artisan would know the limitations of the art, the art is predictable. This might be true insofar as the skilled artisan would be able to predict immediate failure in attempting to practice the majority of embodiments encompassed by the claimed method. However, Applicant is still claiming those embodiments, and with sufficient experimentation those embodiments might one-

day be enabled. Because of the limitations that Applicant acknowledges to exist, the means to make the claimed invention such that it is generally enabled for *in vivo* and *ex vivo* gene therapy would not be readily apparent to the skilled artisan at the time of filing. Therefore, the claims are not enabled for their full scope.

With regard to the particulars of the cited art, Applicant first dismisses the teachings of Verma *et al.* as specifically directed to problems associated with using retroviral vectors (first full paragraph on page 33). However, the statement cited in the previous Office Action (i.e., "[t]he Achilles heel of gene therapy is gene delivery") is a general statement as evidenced by the fact that Verma *et al.* generally discusses "categories of delivery vehicle" in that same paragraph. Thus, Verma *et al.* is clearly addressing gene transfer by any means.

Likewise, Applicant dismisses the teachings of Marshall *et al.* as specifically addressing problems associated with agents such as various viruses and carrier PEG in obtaining efficient gene delivery and expression. However, again it is clear that the statement cited in the previous Office Action (i.e., "difficulties in getting genes transferred efficiently to target cells- and getting the m expressed-remain a nagging problem for the entire field") is generally directed to problems encountered regardless of the gene transfer method used.

To evidence the progress and success of the field of gene therapy between the publication of Marshall et al. and the filing date of the instant application, Applicant provides Mountain (2000) and particularly points to the statement "Within the past year, clinical benefit from gene therapy has been clearly demonstrated for the first time" (page 120, col. 2 paragraph bridging to page 121). The author further states, "the most important recent development in gene therapy is the clear demonstration of efficacy in clinical studies, which might lead to a restoration of public

and investor confidence in gene therapy" (page 126, col. 2, last paragraph). However, these statements are made in the context of the paragraph that immediately precedes them, which states, "it is clear from the first decade of clinical experience that developing effective gene therapies is technically much more demanding than originally anticipated and that the first generation of vectors gave inadequate performance in several respects that are important for achieving clinical benefit with most diseases." Further, Mountain refers to the "successes" as notable exceptions (second full paragraph in the right column on page 120). Thus, even the most optimistic reading of Mountain provides only that gene therapy is generally not enabled with a few notable exceptions. However, the instant claims are not limited to the notable exceptions, but broadly encompass gene therapy in general. According to Mountain, such a broad scope was not within the capabilities of the ordinary skilled artisan.

With regard to Orkin *et al.* Applicant focuses on statements found therein which indicate support for the continued development of the field. However, these statements cannot be taken as evidence that gene therapy was generally enabled at the time of filing (*Id.*) and, in fact, support the Examiner's contention that practicing gene therapy methods requires additional experimentation.

To further rebut the enablement rejection, Applicant submits Cavazzana-Calvo *et al.* (2000) *Science* 238:669-672, which Applicant alleges to describe the clinical efficacy achievements in gene therapy. However, even assuming, *arguendo*, that the treatment of SCID-X1 according to the method of Cavazzana-Calvo *et al.* is fully enabled, the teachings found therein are not enabling for *ex vivo* and *in vivo* gene therapy in general. Somia *et al.* (2000) *Nature Rev. Genet.* 1:91-99, commenting on the findings of Cavazzana-Calvo *et al.*, states, "the

success with SCID-X1 is probably owing to the strong selective advantage provided to the transduced lymphoid progenitors. Only those haemtaopoietic cells that express the γc receptor subunit can survive and differentiate" (page 96, column 1). Further, Somia *et al.* teaches, "[i]t remains to be seen if this approach will work for other diseases, because the success with SCID-XI is probably owing to the strong selective advantage provided to the transduced lymphoid progenitors". Rosen (2002) *N. Engl. J. Med.* 346:1185-1193 expresses even less optimism regarding the degree to which the success obtained in treating SCID-XI can be extended to other diseases. Rosen states, "[p]erhaps...other forms of severe combined immunodeficiency may also benefit from gene therapy in the near future. Then again, this may not prove to be so easy in the case of genes that must be tightly regulated, unlike γc" (paragraph bridging pages 1242 and 1243). Rosen thus implies that even diseases that are closely related will present unique challenges to be overcome in developing gene therapy treatments. Thus, the art viewed as a whole indicates that the success in treating SCID-X1 was in part due to the fact that the disease is particularly amenable to treatment by gene therapy. The results should not be taken as evidence for the enablement of gene therapy for any condition other than SCID-XI, and the successful treatment of SCID-XI cannot be taken as an indication that gene therapy is now a predictable art, or that developing a gene therapy treatment of any given disease could be achieved by routine experimentation.

With regard to Eck *et al.* applicant points to teachings indicating success in gene transfer and expression. However, as pointed out in the previous Office Action, "while it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in

trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect" (page 11). The state of the art of gene therapy is such that achieving expression of a given gene *in vitro* or in an animal system cannot be taken as evidence that therapeutic effect can be achieved with that particular expression system, and clearly cannot be taken as evidence of enablement for claims that broadly encompass gene therapy of any condition.

With regard to Rubanyi *et al.* Applicant contends that the reference cite a number of successes of gene therapy as of 2001 and argues that the need for improvements, which is a constant need in any field, does not signal lack of enablement but rather the search for betterment of an already established art. However, most of these "successes" are limited to animal model systems, which have not been found to accurately predict successful gene therapy in humans; and, as pointed out in the previous Office Action, Rubanyi generally teaches, "so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Thus, Rubanyi teaches that, in general, therapeutic methods comprising delivery of nucleic acids are not enabled. Thus, the teachings found in Rubanyi *et al.* do not support enablement for the full scope of a method that generally encompasses gene therapy.

Applicant criticizes the citation of Rubanyi's statement, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" as being taken out of context. Applicant argues, "the statement is set forth in the context of how one may overcome technical hurdles in clinical trials by selecting a disease target of interest such as CAD and then examining all of the success criteria such as availability of therapeutic genes,

gene delivery, gene expression, lack of unwanted reactions to therapy, clinically relevant effect in animal models, appropriate safety in Phase I and significant therapeutic effect in Phase II and Phase III clinical trials" (page 44). However, it is precisely the Examiner's point that each and every application of gene therapy to the treatment of a given disease will pose its own set of problems which must be overcome by the addressing each of the criteria identified by Rubanyi. As these problems had been successfully addressed in very few, if any, of the diseases that might one day be treated by gene therapy at the time of filing, gene therapy could not be considered as a generally enabled method. Furthermore, a general teaching of how to deliver a large nucleic acid into a cell does not adequately enable a method that generally encompasses *ex vivo* and *in vivo* gene therapy. Applicant concludes "contrary to the Examiner's assertion, the teachings of Rubanyi et al. demonstrate the feasibility of gene therapy methods and further demonstrate that it is possible to predictably and systematically address limitations of gene therapy to improve its efficacy" (page 44). However, the feasibility of gene therapy is not at issue. Enablement under 35 U.S.C. §112, first paragraph, requires not only that the clamed invention be feasible, but that the skilled artisan can make and use the claimed invention in accordance with the full scope of the claims. Given the conclusory statements of Rubanyi *et al.*, characterizing the state of the art as "still in its infancy" and in its "development phase" (first paragraph on page 136), the skilled artisan would not have viewed the art as generally enabling for gene therapy as it is encompassed by the instant claims.

Applicant dismisses the teachings of Schwaab *et al.*, Rissanen *et al.* and Emanueli *et al.* as irrelevant because "the instant methods are not methods of gene therapy *per se*, much less gene therapy involving particular genes for a particular disease". However, the art was cited

merely to reinforce the point made by Rubanyi *et al.* that any given disease presents a unique set of problems which must be overcome in order to enable gene therapy for that disease. This, in turn, provides evidence for the tremendous amount of experimentation that will be required in order to practice the full scope of the claimed invention as it broadly encompasses *ex vivo* and *in vivo* gene therapy of any condition. Because these problems have been adequately addressed in only a very few instances, gene therapy cannot be considered generally enabled. Although the claims are not limited to gene therapy, the specification makes clear and Applicant acknowledges that *in vivo* and *ex vivo* gene therapy is within the scope of the claimed subject matter.

Applicant also cites teachings found in Schwaab *et al.*, Rissanen *et al.* and Emanueli *et al.* which are characterized as "establishing proof of principle for gene therapy". However, enablement under 35 U.S.C. §112, first paragraph, requires more than "proof of principle", which is more in line with the utility requirement of 35 U.S.C. §101. Instead, the enablement requirement of 35 U.S.C. §112, first paragraph, requires that the manner and process of making and using the claimed invention be described in such full, clear, concise, and exact terms as to enable any person skilled in the relevant art to make and use the invention commensurate with its full scope. Clearly, the disclosure fails to enable the claims for the full scope of the method, as it is practiced *ex vivo* or *in vivo*.

Applicant's arguments have been fully considered but are not found persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claims.

Claim Rejections - 35 USC § 102

Claims 1, 3-10, 12-14, 30-33 were rejected under 35 U.S.C. 102(b) as being anticipated by Hadlaczky *et al.* (February 2000) U.S. Patent No. 6,025,155.

In response to the rejection of record, Applicant argues that Hadlaczky *et al.* does not disclose methods that include sequential exposure of a nucleic acid to a delivery agent, a cell to a delivery agent and the nucleic acid to the cell, where the steps are performed sequentially in any order. This argument has been fully considered but is not found persuasive. Although the claim no longer recites that the steps can be performed simultaneously, the claims have been interpreted to encompass the method wherein steps (b) and (c) are performed simultaneously for reason set forth below under Claim Rejections - 35 USC § 112, second paragraph. Therefore, the teachings of Hadlaczky *et al.* still anticipate the claimed subject matter.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33 and 144-146 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "exposing". It is unclear from the disclosure what constitutes exposing a nucleic acid molecule or a cell to a delivery agent. That is, must the

nucleic acid molecule or cell be in physical contact with the delivery agent or is it sufficient that they be in some undefined proximity to one another.

Claim 1 is also indefinite in reciting that the steps (a)-(c) are performed sequentially in any order. In particular, in many cases (i.e., wherein the delivery agent is a chemical compound) if step (a) is performed first, it would not be possible to perform step (c) second without performing step (b) simultaneously. Therefore, does the requirement that the steps be performed sequentially eliminate the method wherein the steps are carried out in the order (a), (c), (b) from the scope of the claims? Given the broadest reasonable interpretation of "in any order", the claims are understood to encompass the method wherein step (a) precedes step (c), and step (b) happens to coincide with step (c).

Claims 2-33 and 144-146 are indefinite insofar as they depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2-17, 26-28, 30-33, 61-64, 141-144 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadlaczky *et al.* U.S. Patent No. 6,025,155 (already of record) in view of Unger *et al.* (1997) *Invest. Radiol.* 32:723-727 (already of record).

As described in the previous Office Action, Hadlaczky *et al.* teaches that the artificial chromosomes disclosed therein, having a size of 20-30 Mb (Figure 2), can be introduced into cells using lipid mediated transfer (paragraph bridging columns 5 and 6) which one of ordinary skill in the art would understand to comprise: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to the delivery agent; and (c) contacting the cell with the nucleic acid molecule. Thus, Hadlaczky *et al.* teaches all of the limitations of claims 1 and 3-8 except for embodiments wherein one of the delivery agents is energy.

Also as described in the previous Office Action, Unger *et al.* teaches a method for introducing a nucleic acid molecule into a cell comprising: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to a delivery agent; and (c) contacting the cell with the nucleic acid molecule wherein, in step (a) the nucleic acid is exposed to a cationic

compound and in step (b) the cells are exposed to ultrasound (see especially the first and second full paragraphs on page 725 and Figure 4 and the caption thereto). Although in the response Applicant argues that Unger does not teach the method wherein the energy is not applied to the cell after contacting the cell with the nucleic acid molecule, this limitation is actually found in Figure 1, wherein cells were treated with ultrasound 30 minutes before the addition of transfection agent. Thus, Unger *et al.* teaches the limitations of claims 1, 2, 11 and 26-28 except for a large nucleic acid molecule. Unger *et al.* further teaches enhanced gene expression obtained by combining sonoporation with transfection reagents.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of Hadlaczky *et al.* with the teachings of Unger *et al.* to obtain enhanced gene expression. Motivation to combine these teachings is found in Hadlaczky *et al.*, who teaches that the artificial chromosomes described therein are useful for expressing exogenous DNAs in a cell (see especially the fourth paragraph in column 17) and from Unger *et al.* who teaches that ultrasound enhanced gene expression in all of the cell lines tested (see especially Figure 4 and Table 1 and the captions thereto). Given the general desirability of obtaining enhanced gene expression from methods designed for expressing exogenous DNA, the skilled artisan clearly would be motivated to combine the teachings of Hadlaczky *et al.* and Unger *et al.* according to the instant claims.

As described in the previous Office Action, Hadlaczky *et al.* and Unger *et al.* variously teach the limitations of claims 9, 10, 12-17, 30-33, 61-64. Further, the combined teachings of Hadlaczky *et al.* and Unger *et al.* provide all of the components of the kit of claims 141-143. Furthermore, Hadlaczky *et al.* teaches a nucleic acid molecule of about 10 megabases to about

450 megabases of claim 144 and the nucleic acid molecule of about 15 megabases to about 50 megabases of claim 146.

Thus, for the reasons set forth herein above, the invention of claims 1, 2-17, 26-28, 30-33, 61-64 and141-143, 144 and 146, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID GUZO
PRIMARY EXAMINER

DMS